General

Guideline Title

Uterine sarcoma.

Bibliographic Source(s)

Alberta Provincial Gynecologic Oncology Team. Uterine sarcoma. Edmonton (Alberta): CancerControl Alberta; 2013 Sep. 15 p. (Clinical practice guideline; no. GYNE-007). [76 references]

Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: Alberta Provincial Gynecologic Oncology Tumour Team. Uterine sarcoma. Edmonton (Alberta): Alberta Health Services, Cancer Care; 2011 Aug. 14 p. (Clinical practice guideline; no. GYNE-007). [74 references]

Recommendations

Major Recommendations

The Fédération Internationale de Gynecologie et d'Obstétrique (FIGO) staging of sarcomas was updated in 2010. A detailed description of this staging system can be found in the Appendix in the original guideline document.

There was limited high level evidence (e.g., meta-analyses, systematic reviews, or randomized controlled trials) on gynecologic sarcomas available to inform these guidelines. Recommendations were based largely on data from phase II trials, retrospective reviews, case studies, and in some circumstances non-gynecologic sarcomas, as well as expert opinion.

Principles of Staging

Staging investigations may include (in most cases for leiomyosarcoma [LMS] and undifferentiated endometrial sarcoma):

- Preoperative computed tomography (CT) of the abdomen and pelvis to rule out extrauterine disease
- Preoperative CT of the chest to rule out lung metastases

An expert pathology review should be performed by a pathologist with experience in gynecologic and/or sarcoma pathology.

Treatment

Leiomyosarcoma Options

Stage I (Tumour Limited to Uterus)

- Total hysterectomy with bilateral salpingo-oophorectomy (BSO)
- Ovarian preservation may be considered in young women on a case-by-case basis.
- There is no high-level evidence to support the use of post-operative adjuvant radiotherapy or adjuvant chemotherapy.

Stage II (Tumour Extends to the Pelvis)

No standard therapy has been established; options include:

- Neoadjuvant radiotherapy, followed by resection of gross tumour if debulking is achievable
- Neoadjuvant chemotherapy +/- radiotherapy, followed by resection of gross tumour if debulking is achievable
- Resection of gross tumour if debulking achievable; consider adjuvant chemotherapy +/- radiotherapy.

Stage III (Tumour Invades Abdominal Tissues)

No standard therapy has been established; options include:

- Neoadjuvant radiotherapy, followed by resection of gross tumour if debulking is achievable
- Neoadjuvant chemotherapy +/- radiotherapy, followed by resection of gross tumour if debulking is achievable
- Resection of gross tumour if debulking achievable; consider adjuvant chemotherapy +/- radiotherapy.

Stage IVA (Tumour Invades Bladder and/or Rectum)

- Neoadjuvant radiotherapy, followed by resection of gross tumour if debulking is achievable
- Neoadjuvant chemotherapy +/- radiotherapy, followed by resection of gross tumour if debulking is achievable
- Palliative chemotherapy may be used in patients for whom surgery is not an option.
- Palliative radiotherapy may be used for specific symptom control (e.g., bleeding, pain).

Stage IVB (Distant Metastasis)

- In select patients with limited metastatic disease, neoadjuvant radiotherapy or neoadjuvant chemotherapy, followed by debulking surgery can be considered. For isolated lung metastases, consider referral to a thoracic surgeon for resection.
- Palliative chemotherapy may be used in patients for whom surgery is not an option.
- Palliative radiotherapy may be used for specific symptom control (e.g., bleeding, pain).

Palliative Chemotherapy Options

- There is no standard chemotherapy regimen.
- Agents that have been used include: doxorubicin, ifosfamide, gemcitabine, docetaxel, trabectedin, dacarbazine, and cisplatin.
- Combination chemotherapy should be used only in fit patients.

Recurrent Disease

- Surgery for localized disease
- Chemotherapy followed by CT scan to determine disease response
- Palliative radiotherapy for specific symptom indication (e.g., bleeding, pain)

Where possible, patients should be considered for enrolment in a clinical trial.

Adenosarcoma Options

- Total hysterectomy with BSO
- Resection of gross tumour in advanced cases, if debulking is achievable

Adjuvant treatment is not typically required.

Where possible, patients should be considered for enrolment in a clinical trial.

Endometrial Stromal Sarcoma (ESS) (Formerly Low-grade ESS) Options

- Total hysterectomy with BSO

- Resection of gross tumour in advanced cases, if debulking is achievable
- Post-operative hormonal therapy (typically Megestrol acetate) in patients with advanced or metastatic disease

Where possible, patients should be considered for enrolment in a clinical trial.

Undifferentiated Endometrial Sarcoma (Formerly High-grade ESS) Options

Stage I (Tumour Limited to Uterus)

- Total hysterectomy with BSO
- Selective biopsy of pelvic +/- para-aortic lymph nodes

Stage II (Tumour Extends to the Pelvis)

- Total hysterectomy with BSO
- Resection of gross tumour if debulking is achievable

Stage III (Tumour Invades Abdominal Tissues)

- Total hysterectomy with BSO
- Resection of gross tumour if debulking is achievable

Stage IVA (Tumour Invades Bladder and/or Rectum)

- Resection of gross tumour if debulking is achievable
- Neoadjuvant chemotherapy can be considered, followed by debulking surgery.
- Palliative radiotherapy, if surgery is not an option
- Palliative chemotherapy, if surgery is not an option

Stage IVB (Distant Metastasis)

- Neoadjuvant chemotherapy, followed by debulking surgery; refer patient to a thoracic surgeon for resection of isolated lung metastases.
- Palliative chemotherapy and/or radiotherapy if surgery is not an option
- Palliative radiotherapy may be used for specific symptom control (e.g., bleeding, pain).
- Palliative chemotherapy may be used in patients who have unresectable disease.

Palliative Chemotherapy Options

- There is no standard chemotherapy regimen.
- Agents that have been used include: doxorubicin, ifosfamide, gemcitabine, docetaxel, dacarbazine, and cisplatin.
- Combination chemotherapy should be used only in fit patients.

Recurrent Disease

- Surgery for localized disease
- Chemotherapy followed by CT scan to determine disease response
- Palliative radiotherapy for specific symptom indication (e.g., bleeding, pain)
- Palliative chemotherapy may be used in patients who have unresectable disease.

Where possible, patients should be considered for enrolment in a clinical trial.

Hormone Therapy

For patients whose tumours express estrogen and/or progesterone receptors, consider a trial of hormone therapy (e.g., palliative setting): gonadotropin releasing hormone (GnRH) analogs (i.e., leuprolide, zoladex), aromatase inhibitors (i.e., anastrozole, letrozole) and progestins (i.e., medroxyprogesterone acetate, megestrol acetate).

Follow-up

- Regular chest x-ray is recommended; other imaging investigations should be performed, only as clinically indicated.
- Follow-up visits should typically occur every 3 to 6 months during years 1 and 2 and then annually for years 3-5.

- Follow-up visits can also be planned according to risk stratification (i.e., tumour grade, size, and site):
  - Intermediate/high-risk patients could be seen every 3 to 4 months for the first 2 to 3 years and annually thereafter.
  - Low-risk patients could be seen every 4 to 6 months for the first 3 to 5 years and annually thereafter.

Clinical Algorithm(s)

An algorithm titled "Algorithm for the Diagnosis & Management of Uterine Sarcoma (GYNE-007)" is provided on the Alberta Health Services Web site .

Scope

Disease/Condition(s)

Uterine sarcoma

- Leiomyosarcoma
- Adenosarcoma
- Endometrial stromal sarcoma (ESS) (formerly low-grade ESS)
- Undifferentiated endometrial sarcoma (formerly high-grade ESS)

Note: This guideline does not cover carcinosarcoma, which should be staged as carcinoma of the endometrium. For recommendations on the management of endometrial carcinosarcoma, please refer to the National Guideline Clearinghouse summary of the Alberta Health Services guideline Endometrial cancer.

Guideline Category

Evaluation

Management

Treatment

Clinical Specialty

Obstetrics and Gynecology

Oncology

Pathology

Radiation Oncology

Surgery

Intended Users

Clinical Laboratory Personnel

Physicians

Guideline Objective(s)

To recommend options for the management of uterine sarcoma, based on the best evidence available

Target Population

Adults over the age of 18 years with uterine sarcoma, including leiomyosarcoma and endometrial stromal sarcoma

Interventions and Practices Considered

Evaluation (Staging Investigations)

1. Preoperative computed tomography (CT) of the abdomen and pelvis
2. Preoperative CT of the chest
3. Expert pathology review

Treatment/Management

1. Total hysterectomy with bilateral salpingo-oophorectomy (BSO)
2. Consideration of ovarian preservation in young women
3. Neoadjuvant radiotherapy, followed by debulking surgery
4. Neoadjuvant chemotherapy +/- radiotherapy followed by debulking surgery
5. Resection of gross tumour if debulking achievable, followed by chemotherapy +/- radiotherapy
6. Palliative chemotherapy
7. Palliative radiotherapy
8. Referral for resection of isolated lung metastases
9. Chemotherapy options: doxorubicin, ifosfamide, gemcitabine, docetaxel, trabectedin, dacarbazine, and cisplatin
10. Treatment of recurrent disease (surgery for localized disease, chemotherapy followed by CT scan to determine disease response, palliative radiotherapy for specific symptom indication, palliative chemotherapy)
11. Enrolment in a clinical trial
12. Hormone therapy: gonadotropin releasing hormone (GnRH) analogs, aromatase inhibitors, and progestins
13. Follow-up investigations

Major Outcomes Considered

- Survival rate (5-year, overall, progression-free)
- Pelvic recurrence rate
- Local control

Methodology

Methods Used to Collect/Select the Evidence

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

Research Questions

Specific research questions to be addressed by the guideline document were formulated by the guideline lead(s) and Knowledge Management (KM) Specialist using the PICO question format (Patient or Population, Intervention, Comparisons, Outcomes).

Guideline Questions

- What is the optimal surgical staging for leiomyosarcoma?
- What is the role of adjuvant chemotherapy and/or radiotherapy for leiomyosarcoma?
- For leiomyosarcoma, is there a role for hormonal adjuvant therapy?

- What treatment options exist for metastatic or recurrent leiomyosarcoma?
- What are the best management options for adenosarcoma?
- What is the optimal surgical staging for endometrial stromal sarcoma and undifferentiated endometrial sarcoma?
- What is the role of adjuvant chemotherapy and/or radiotherapy for endometrial stromal sarcoma and undifferentiated endometrial sarcoma?
- For endometrial stromal sarcoma and undifferentiated endometrial sarcoma, is there a role for hormonal adjuvant therapy?
- What treatment options exist for metastatic or recurrent endometrial stromal sarcoma and undifferentiated endometrial sarcoma?

Search Strategy

Entries to Medline and EMBASE and clinical practice guideline databases (e.g., National Guideline Clearinghouse, CancerView, etc.) were searched for evidence relevant to this topic. Search terms included: leiomyosarcoma or adenosarcoma uterine or endometrial stromal sarcoma AND bilateral salpingo-oophorectomy or total abdominal hysterectomy or lymphadenectomy or surgery or surgical resection or chemotherapy or radiotherapy or megestrol acetate or medroxyprogesterone or progestin. Among the relevant studies returned by the search, those that did not report response rates or survival rates were further excluded.

The original search returned a total of 86 studies, including clinical trials, retrospective studies, and case studies, which were included in the review. The 2013 update of the literature returned a total of 10 new studies which were considered when reviewing the recommendations.

Existing guidelines considered for this review include the following: the National Comprehensive Cancer Network (NCCN) guidelines (2010), the BC Cancer Agency (BCCA) guidelines (2000), the National Cancer Institute guidelines (2008) and the Tom Baker Cancer Centre guidelines (2008).

Number of Source Documents

Not stated

Methods Used to Assess the Quality and Strength of the Evidence

Not stated

Rating Scheme for the Strength of the Evidence

Not applicable

Methods Used to Analyze the Evidence

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

Evidence was selected and reviewed by a working group comprised of members from the Alberta Provincial Gynecologic Oncology Tumour Team and a Knowledge Management (KM) Specialist from the Guideline Utilization Resource Unit (GURU). A detailed description of the methodology followed during the guideline development process can be found in the Guideline Utilization Resource Unit Handbook (see the "Availability of Companion Documents" field).

Evidence Tables

Evidence tables containing the first author, year of publication, patient group/stage of disease, methodology, and main outcomes of interest are assembled using the studies identified in the literature search. Existing guidelines on the topic are assessed by the KM Specialist using portions of the Appraisal of Guidelines Research and Evaluation (AGREE) II instrument (http://www.agreetrust.org) and those meeting the minimum requirements are included in the evidence document. Due to limited resources, GURU does not regularly employ the use of multiple reviewers to rank the level of evidence; rather, the methodology portion of the evidence table contains the pertinent information required for the reader to judge for himself the quality of the studies.

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

Formulating Recommendations

The working group members formulate the guideline recommendations based on the evidence synthesized by the Knowledge Management (KM) Specialist during the planning process, blended with expert clinical interpretation of the evidence. As detailed in the Guideline Utilization Resource Unit Handbook (see the "Availability of Companion Documents" field), the working group members may decide to adopt the recommendations of another institution without any revisions, adapt the recommendations of another institution or institutions to better reflect local practices, or develop their own set of recommendations by adapting some, but not all, recommendations from different guidelines.

The degree to which a recommendation is based on expert opinion of the working group and/or the Provincial Tumour Team members is explicitly stated in the guideline recommendations. Similar to the American Society of Clinical Oncology (ASCO) methodology for formulating guideline recommendations, the Guideline Utilization Resource Unit (GURU) does not use formal rating schemes for describing the strength of the recommendations, but rather describes, in conventional and explicit language, the type and quality of the research and existing guidelines that were taken into consideration when formulating the recommendations.

An effort was made to either adapt or adopt the most appropriate guidelines from other sources so that work wasn't duplicated. An evidence-based perspective was used to draft proposals. Where evidence was weak, recommendations were based on group consensus.

Rating Scheme for the Strength of the Recommendations

Not applicable

Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

Internal Peer Review

Description of Method of Guideline Validation

This guideline was reviewed and endorsed by the Alberta Provincial Gynecologic Oncology Tumour Team.

When the draft guideline document has been completed, revised, and reviewed by the Knowledge Management (KM) Specialist and the working group members, it will be sent to all members of the Provincial Tumour Team for review and comment. This step ensures that those intended to use the guideline have the opportunity to review the document and identify potential difficulties for implementation before the guideline is finalized. Depending on the size of the document, and the number of people it is sent to for review, a deadline of one to two weeks will usually be given to submit any feedback. Ideally, this review will occur prior to the annual Provincial Tumour Team meeting, and a discussion of the proposed edits will take place at the meeting. The working group members will then make final revisions to the document based on the received feedback, as appropriate. Once the guideline is finalized, it will be officially endorsed by the Provincial Tumour Team Lead and the Executive Director of Provincial Tumour Programs.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

There was limited high level evidence (e.g., meta-analyses, systematic reviews, or randomized controlled trials) on gynecologic sarcomas available to inform these guidelines. Recommendations were based largely on data from phase II trials, retrospective reviews, case studies, and in some circumstances non-gynecologic sarcomas, as well as expert opinion.

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Appropriate management of patients with uterine sarcoma

Potential Harms

Combination chemotherapy is far more toxic than gemcitabine alone and the most common toxicities associated with gemcitabine and docetaxel were thrombocytopenia (14.5%–39.4%), neutropenia (17%–20.8%), and anemia (24%–25%).

Qualifying Statements

Qualifying Statements

The recommendations contained in this guideline are a consensus of the Alberta Provincial Gynecologic Oncology Team and are a synthesis of currently accepted approaches to management, derived from a review of relevant scientific literature. Clinicians applying these guidelines should, in consultation with the patient, use independent medical judgment in the context of individual clinical circumstances to direct care.

Implementation of the Guideline

Description of Implementation Strategy

- Present the guideline at the local and provincial tumour team meetings and weekly rounds.
- Post the guideline on the Alberta Health Services website.
- Send an electronic notification of the new guideline to all members of CancerControl Alberta.

Implementation Tools

Clinical Algorithm

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

Living with Illness

IOM Domain

Effectiveness

Identifying Information and Availability

Bibliographic Source(s)

Alberta Provincial Gynecologic Oncology Team. Uterine sarcoma. Edmonton (Alberta): CancerControl Alberta; 2013 Sep. 15 p. (Clinical practice guideline; no. GYNE-007). [76 references]

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2011 Aug (revised 2013 Sep)

Guideline Developer(s)

CancerControl Alberta - State/Local Government Agency [Non-U.S.]

Source(s) of Funding

CancerControl Alberta

There was no direct industry involvement in the development or dissemination of this guideline.

Guideline Committee

Alberta Provincial Gynecologic Oncology Team

Composition of Group That Authored the Guideline

Members of the Alberta Provincial Gynecologic Oncology Tumour Team include gynecologic oncologists, radiation oncologists, medical oncologists, pathologists, nurses, and pharmacists.

Financial Disclosures/Conflicts of Interest

Participation of members of the Alberta Provincial Gynecologic Oncology Team in the development of this guideline has been voluntary and the authors have not been remunerated for their contributions. CancerControl Alberta recognizes that although industry support of research, education and other areas is necessary in order to advance patient care, such support may lead to potential conflicts of interest. Some members of the Alberta Provincial Gynecologic Oncology Team are involved in research funded by industry or have other such potential conflicts of interest. However the developers of this guideline are satisfied it was developed in an unbiased manner.

Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: Alberta Provincial Gynecologic Oncology Tumour Team. Uterine sarcoma. Edmonton (Alberta): Alberta Health Services, Cancer Care; 2011 Aug. 14 p. (Clinical practice guideline; no. GYNE-007). [74 references]

Guideline Availability

Electronic copies: Available in Portable Document Format (PDF) from the Alberta Health Services Web site .

Availability of Companion Documents

The following is available:

- Guideline utilization resource unit handbook. Edmonton (Alberta): CancerControl Alberta; 2013 Jan. 5 p. Electronic copies: Available in Portable Document Format (PDF) from the Alberta Health Services Web site .

Patient Resources

None available

NGC Status

This NGC summary was completed by ECRI Institute on December 19, 2012. The information was verified by the guideline developer on February 1, 2013. This summary was updated by ECRI Institute on April 28, 2014. The updated information was verified by the guideline developer on June 6, 2014. This summary was updated by ECRI Institute on July 18, 2014 following the U.S. Food and Drug Administration advisory on Docetaxel.

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